RECEIVED
CENTRAL FAX CENTER

NOV 13 2006

REMARKS

New Claims 70-84 have been added to point out with greater clarity and particularity the subject matter regarded by the Applicants as their invention. Applicants respectfully submit that new Claims 70-84 are supported throughout the Specification.

New Claims 70-82 are directed to a diagnostic/prognostic method for a preneoplastic/neoplastic disease associated with abnormal MN/CA IX expression, comprising determining whether MN/CA IX is activated in a vertebrate sample, wherein binding of a specific inhibitor of activated MN/CA IX indicates that MN/CA IX is activated. General support for the detection of activated MN/CA IX using specific inhibitors as a diagnostic/prognostic method is found in the Specification at the least at page 1, lines 18-21; at page 8, line 24 to page 9, line 31; at page 23, line 27 to page 24, line 21; at page 25, line 11 to page 27, line 6; at page 28, lines 6-14; and at page 91, lines 12-25 (original claims 67-68).

Particular support for Claims 70-82 is found at page 9, lines 10-31, which reads in part:

> CA IX was found by the inventors also to contribute to acidification of extracellular pH in hypoxia but not in normoxia. . . . **The latter result indicates that . . . hypoxia activates the CA catalytic activity of CA IX. . . .** The instant invention is related to (1) the recognition that **certain carbonic anhydrase inhibitors (CAIs),** preferably sulfonamides, **selectively target the cancer-related, hypoxia-induced MN/CA IX.** . . . ; and (4) the use of the specificity of potent MN/CA IX-specific inhibitors for diagnostic/prognostic methods including imaging methods. . . .

[Emphasis added.] Additional particular support can be found in the Specification at page 27, lines 1-6, which describes transfection experiments showing that CA IX-specific inhibitors did not bind to overexpressed MN/CA IX under normoxic conditions, but did bind overexpressed MN/CA IX under hypoxic conditions, indicating that the CA IX-specific inhibitors only bind to activated MN/CA IX:

> Further, labeled exemplary CA IX-specific inhibitors, such as labeled sulfonamides, for example, conjugated to fluorescein isothiocyanate (FITC), are shown to bind to the surface of MN/CA IX transfected cells, and not to control cells, only in

> hypoxia but not in normoxia. Those experiments confirm that CA IX-specific inhibitors, such as the sulfonamide compounds described herein, can specifically target MN/CA IX under conditions characteristic of intratumoral microenvironments.

[Instant Specification; at page 27, lines 1-6.]

Support for the MN/CA IX-specific sulfonamide inhibitors of new Claims 72-75 can be found in the Specification at the least at page 12, line 24 to page 16, line 2; at page 18, line 6 to page 22, line 27; and at page 59, line 24 to page 70, line 6, particularly at Tables 1-3, wherein the inhibition constants [K_I] of MN/CA IX inhibition by sulfonamide compounds **1-91** are provided. Particular support for Claims 76-77, wherein the specific inhibitor of activated MN/CA IX is conjugated to a label, can be found in the Specification at page 27, lines 1-6 (cited above).

Support for new Claims 78-82, wherein the diagnostic/prognostic method is used as an aid in patient therapy selection, can be found in the Specification at the least at page 23, line 27 to page 24, line 13, particularly at page 24, lines 9-13, which reads:

> MN/CA IX as a hypoxia marker is useful in general in making therapeutic decisions. For example, a cancer patient whose tumor is known to express MN/CA IX at an abnormally high level would not be a candidate for certain kinds of chemotherapy and radiotherapy, but would be a candidate for hypoxia-selective chemotherapy.

And at page 28, lines 6-12, which reads:

> Particularly, the CA IX-specific inhibitors of this invention can be used diagnostically/prognostically to detect precancerous and/or cancerous cells by binding to CA IX, preferably to CA IX activated by hypoxic conditions, wherein said CA IX specific inhibitors are coupled to a label or to some visualizing means. Such detection, particularly of hypoxic conditions, and CA IX overexpression, can be helpful in determining effective treatment options, and in predicting treatment outcome and the prognosis of disease development.

Further particular support for Claims 81 and 82, wherein the method is used in the decision to use hypoxia-selective therapy, preferably drugs that are toxic only under

hypoxic conditions, still more preferably tirapazamine and AQ4N, can be found in the Specification at page 24, lines 18-21.

New Claims 83-84 are directed to a method of imaging hypoxic tissues in a patient, comprising the use of specific inhibitors of activated MN/CA IX, preferably MN/CA IX-specific sulfonamides. Particular support for new Claims 83-84 can be found in the Specification at the least at page 28, lines 10-14, which reads:

> Such detection, particularly of hypoxic conditions, and CA IX overexpression, can be helpful in determining effective treatment options, and in predicting treatment outcome and the prognosis of disease development. Further the CA IX-specific inhibitors when labeled or linked to an appropriate visualizing means can be used for imaging tumors and/or metastases that express CA IX.

Applicants respectfully conclude that no new matter has been entered by any of the above amendments.

CONCLUSION

Applicants respectfully submit that the pending Group VII Claims 67-69 and new Claims 70-84 are in condition for allowance and earnestly request that Claims 67-84 be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,

Leona L. Lauder
Attorney for Applicants
Registration No. 30,863

Dated: November 13, 2006